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Toward Personalized Medicine: Does Genetic Diagnosis of Pediatric Cardiomyopathy Influence Patient Management?

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Abstract

A goal of personalized medicine is to provide increasingly sophisticated, individualized approaches to management and therapy for disease. Genetics is the engine that drives personalized medicine, holding the promise of therapeutics directed toward the unique needs of each patient. The 3rd International Conference on Cardiomyopathy in Children provided a forum to discuss the current status of personalized approaches to diagnosis, management, and therapy in the pediatric cardiomyopathy population. This review will focus on the importance of genetic diagnosis in this population as a necessary first step toward understanding the best approach to management and influencing disease outcome. The genetic heterogeneity of cardiomyopathy in children, the implications of specific genotypes, the ability to risk stratify based on genotype, and the impact on cascade screening in family members will be discussed.

Keywords

sarcomere; syndrome; metabolic; cascade screening

Introduction

The prognosis, response to treatment, and long term outcome of diseases with substantial phenotypic heterogeneity are difficult to predict. Heart muscle disease in infants and children has an extremely variable clinical course with differences in age of onset, response to medication, morbidity and mortality [1–7]. As a result, biomarkers that correlate with clinical outcome, screening that allows earlier identification of disease, genetic testing that allows risk stratification, and diagnostic testing that aids prediction of response to treatment are all approaches that are being intensively investigated with hopes of providing improved management and therapy. With advances in genetic diagnostics, the ability to identify the

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underlying cause of cardiomyopathy in pediatric patients has expanded tremendously. However, the large number of genetic causes of pediatric cardiomyopathy poses a challenge for diagnosis and limits the ability to understand phenotypic variability and longitudinal clinical course. We maintain that understanding genetic causation in this population is a necessary prerequisite toward the development of more specific therapy and an important aspect of creating increasingly personalized medical approaches.

Classification of pediatric cardiomyopathy and etiologic categories

As with adult cardiomyopathy, pediatric cardiomyopathy is typically classified by cardiac phenotype with five major classifications being recognized: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction cardiomyopathy (LVNC)[8]. The latter can be seen alone or in combination with other types of cardiomyopathy, frequently HCM or DCM. These diseases of the myocardium result in systolic dysfunction, diastolic dysfunction, or both, and the clinical taxonomy informs management but does not address the underlying etiology. In adults, HCM is considered a disease of the sarcomere, and is frequently caused by mutations in genes encoding the components of the contractile apparatus. With a prevalence of 1 in 500, HCM is the most common monogenic cardiac disorder [9]. Similarly, non-ischemic DCM is frequently genetic and can be caused by mutations in the contractile apparatus or cytoskeletal components of the myocyte.

Cardiomyopathy also affects infants and children, and while less prevalent than adult cardiomyopathy, it is a chronic and often progressive disease with significant morbidity. Forty percent of affected individuals progress to death or transplant within 5 years of diagnosis. In the pediatric population, cardiomyopathy is most frequently the result of genetic or infectious etiologies [10–12]. There is greater heterogeneity of genetic causes than seen in the adult population, despite similar phenotypic classes of cardiomyopathy. The ability to predict longitudinal clinical course and disease progression would provide new avenues for management and treatment.

In 1994, the Pediatric Cardiomyopathy Registry (PCMR) initiated studies on the epidemiologic features of cardiomyopathy in children with diagnostic categories that included myocarditis, inborn errors of metabolism, malformation syndromes, neuromuscular disease, familial, and unknown (idiopathic) causes [13]. These data pre-dated many clinically available genetic tests and up to 70% of cases were designated idiopathic, but these studies provided a useful framework for understanding the variable causes underlying pediatric cardiomyopathy. In 2012, we performed a single site study in order to determine the etiologic classification of pediatric cardiomyopathy cases when combining recent clinically available genetic testing and full evaluation by clinical geneticists [12]. This study indicated that while mutations in genes that underlie adult cardiomyopathy are common in the infant and pediatric populations, genetic syndromic cases and inborn errors of metabolism, including mitochondrial disorders, comprise up to 30% of causes. In the majority of cases, cardiac imaging does not provide information to assist with distinguishing the underlying etiology. Therefore, history, physical exam, and a comprehensive differential are necessary.

Importantly, patients with these disorders have medical management needs beyond their cardiac care needs and thus precise diagnosis of underlying etiology is critical to optimize treatment.

Benefits of a genetic diagnosis

Clinical genetic testing is currently available for HCM, DCM, RCM, ARVC, and LVNC in the form of large multi-gene panels. These panels primarily test sarcomeric and cytoskeletal gene mutations underlying "familial" cardiomyopathy in HCM, DCM, RCM, and LVNC, and test desmosomal genes in ARVC. Despite expanding gene panels, the yield of testing for HCM has not changed substantially since clinical testing became available in the United States. This is in part due to the fact that mutations in *MYBPC3* and *MYH7* account for the majority of cases of gene positive HCM. Unlike HCM, no gene(s) account for the majority of cases of gene positive DCM, although recent evidence suggests that mutations in *TTN*, encoding the large protein titin, may underlie up to 20% of cases [14]. However, interpretation of variants in this gene are problematic and there is some suggestion that *TTN* may function as a modifier in combination with other genetic variation. Currently, these large multigene panels do not include the most frequently identified causes of syndromic or metabolic disease in the pediatric population such as Noonan syndrome, Alstrom syndrome, Pompe disease or other storage disorders, or mitochondrial disorders. Thus, to investigate these potential causes, they must be considered in the differential of the infant or child with cardiomyopathy and appropriate diagnostic testing performed.

There are several benefits of obtaining a genetic diagnosis in patients with cardiomyopathy, including confirming the diagnosis in ambiguous cases, defining the etiologic basis in order to further guide management, and identifying at risk relatives. In cases where a definitive diagnosis is unclear, such as unexplained left ventricular hypertrophy, positive genetic testing resolves ambiguity and allows institution of appropriate screening and medical therapy, recommendations about physical activity, and institution of appropriate family surveillance. A limitation to this testing is the fact that negative results are not informative and do not rule out a genetic diagnosis.

A second benefit is accurately identifying etiology. This allows for the institution of appropriate cardiac screening and medical therapy, appropriate management and surveillance of other organ system involvement, provision of specific prognostic information, and institution of appropriate family screening and counseling. However, it is important to note that despite a comprehensive diagnostic evaluation, in some instances idiopathic cases remain. In addition, within the distinct etiologic categories, genotype-phenotype correlations are variable and may not impact management.

A third benefit is the ability to identify at risk relatives, thus achieving important risk stratification and allowing cost-effective implementation of cardiac surveillance only in at risk individuals. In the Netherlands, the national healthcare system and the existence of a founder mutation in *MYBPC3* has resulted in broadly instituted genetic testing for HCM with cascade genetic testing provided to first degree relatives [15, 16]. This has led to the diagnosis of presymptomatic individuals at risk for HCM. In the United States, a recent

study investigated the uptake of cardiac screening and genetic screening amongst 302 at risk family members of patients with HCM or DCM [17]. Not surprisingly, first degree relatives were more likely than second degree relatives to complete screening and testing. There was a statistically greater uptake of cardiac surveillance as compared to genetic testing, for unknown reasons. Importantly, 40% of asymptomatic relatives were given a genetic diagnosis and 25% were given a clinical diagnosis based on cardiac imaging. Potential consequences of this cascade screening are improved risk stratification, reduction in sudden cardiac death, improved understanding of early signs and symptoms and disease progression, and a reduction in healthcare costs. However, limitations include logistics for broad implementation and expense. In addition, more research is required to better understand specific motivations and barriers to genetic screening in this population, given the difference in uptake between genetic screening and cardiac screening.

Consensus guidelines on cardiac and genetic screening

Recommendations and consensus guidelines for management of cardiomyopathy incorporating genetic testing and screening of family members have emerged concomitant with the increasing availability of clinical genetic testing [18–22]. Educating patients and families about potential genetic etiologies and inheritance are important components. In addition, specific recommendations about cardiac screening of at-risk relatives and implications of clinical genetic testing should be provided. It is likely that the expertise for these services exists primarily at large academic medical centers.

A 2011 international consensus statement addressed genetic testing guidelines for the five major subtypes of cardiomyopathy (Table 1)[18]. In this document, based on expert option, the strongest recommendation for genetic testing is among patients with HCM where the positive predictive value of testing is high and genetic test results can aid in diagnosis and disease management.

HCM currently has the highest yield of genetic testing with mutations found in upwards of 60% of cases. Therefore, comprehensive or targeted genetic testing is recommended (Class I) for any patient with a clinical diagnosis of HCM. Genetic testing is not currently recommended (Class III) in the evaluation of hypertrophy in an athlete’s heart.

For patients with DCM, genetic testing has a Class I recommendation in cases that also have significant conduction disease and/or a family history of premature sudden cardiac death. Otherwise for those with familial disease, genetic testing can be useful (Class IIa). Similarly, LVNC and ARVC genetic testing has a Class IIa recommendation. Specifically, ARVC genetic testing can be particularly problematic as some genetic variants have also been identified in 13.9–16% of normal, healthy volunteers[23]. Furthermore, many variants which were initially thought to either be pathogenic or benign have been reclassified making testing interpretation particularly challenging for this subclass. Genetic testing may be considered (Class IIb) in RCM, and several new causes of RCM have been identified since the publication of the consensus statement [24–26].

Mutation-specific cascade genetic testing is universally recommended for family members regardless of clinical status after a causative mutation is identified in an index case. This

recommendation is based on the potential for therapeutic or protective intervention in cardiomyopathy. It is also important to note that genetic counseling is recommended in all cases. There should be a thorough discussion of the different genetic testing options and the risks and benefits of such testing. Actual genetic practices vary from center to center and from physician to physician. Decisions to test or not are often tailored to each specific patient or family. Genetic testing may also be influenced by physician knowledge of clinical genetics and ease of genetic testing. Particularly in the pediatric population, genetic testing can be of great importance [9, 12, 19, 27]. Genetic test results can help refine risk stratification and can lead to earlier disease detection and treatment which is especially impactful in young children.

Those individuals who are asymptomatic but found to carry a disease-causing mutation should undergo routine clinical screening [20]. For HCM, screening is recommended every 3 years during until age 30 and then every 5 years. During puberty, screening is increased to yearly. For DCM, LVNC, and RCM clinical screening is yearly in childhood and then every 1–3 years in adulthood. For ARVC, screening is recommended on a yearly basis from age 10 to 50 years. Again, actual clinical practices vary and should be tailored to each specific patient and family.

Current state of the art in genotype-phenotype correlations

A goal of personalized medicine is to apply specific management or therapy to a patients underlying cause of disease. In pediatric cardiomyopathy, the genetic basis of disease is increasingly identified, especially with comprehensive evaluation as discussed previously. The ability to tailor therapy to a specific genetic variant is not currently available and genotype-phenotype correlations are generally limited, in part because most families have unique, private mutations. In a few select cases there are certain genotype-phenotype correlations, but usually there are more exceptions than definitive rules. In HCM, *MYBPC3* mutations were initially reported to have a later age of onset with delayed clinical expression of disease until middle or old age with survival tending to be better than for other sarcomeric gene mutations. However, these results did not incorporate a large number of pediatric cases, and in our anecdotal experience, *MYBPC3* mutations are as common in the pediatric population presenting with cardiomyopathy as *MHY7* mutations. There does appear to be an association between mutation type and number with truncating mutations and more than one mutation being associated with greater disease severity [28, 29].

Patients with *TNNT2* mutations have been reported with relatively small degrees of hypertrophy but with significant rhythm disturbances and a high incidence of sudden cardiac death. *DES* and *LMNA* mutations are also associated with an increased risk of sudden cardiac death [30]. *LMNA* is an example of a gene in which there is significant phenotypic heterogeneity depending on the site of the mutation. The group of disorders caused by mutations in this gene range from muscular dystrophies to premature aging syndromes. Patients with *LMNA* mutations may present with DCM with conduction system disease, or may have skeletal muscle myopathy in the form of limb girdle muscular dystrophy or Emery-Dreifuss muscular dystrophy. Some patients with *LMNA* mutations have ongoing risk for cardiometabolic derangement, including a lipodystrophic phenotype with truncal

adiposity, hyperinsulinemia, and liver dysfunction. Thus, specific clinical surveillance is indicated and patients with DCM resulting from specific *LMNA* variants would have different management based on their genotype than patients with DCM resulting from, for example, *MYH7* variants. In ARVC, *PKP2* mutations seem to be associated with an earlier onset of arrhythmias [31]. Mutations in *PKP2*, *DES*, or *LMNA* should prompt consideration for more frequent screening or even prophylactic defibrillator placement. As a final example, mutations in *DSP*, a desmosomal gene, cause ARVC in approximately 90% of cases and DCM in 10%. All DCM mutations in *DSP* to date are missense mutations. Because the evaluation, surveillance, and management recommendations differ for DCM versus ARVC, these potential genotype-phenotype correlations are important.

Despite some advances, there is still much that needs to be understood in terms of the molecular mechanisms that help determine disease phenotype. Current research efforts are aimed at advancing our understanding of genotype-phenotype correlations including a current NHLBI pediatric study looking at genetic modifiers in patients with known disease causing mutations.

Case Examples

Case 1

An 11-year-old boy was referred to cardiology for a murmur. On history, he previously had surgery for myringotomy tubes and surgery for unilateral cryptorchidism. On physical exam, the patient was noted to be in the fifth percentile for height. He had downslanting palpebral fissures with ptosis. He had a low posterior hairline with webbing of the neck. A 15-lead electrocardiogram (ECG) showed normal sinus rhythm, northwest axis, and an incomplete right bundle branch block. Echocardiogram showed a mid-septal bulge of asymmetric hypertrophy without obstruction.

This patient was referred for genetic testing for suspicion of a Noonan-related syndrome. On further discussion with the parents, they admitted they could never figure out why he was so much shorter than his siblings. In addition, while the patient was in a regular class at school he did have an individualized learning plan in place as there were some scholastic difficulties. This case illustrates how genetic syndromes can often be missed especially when children are young and phenotypic characteristics are subtle. In this case, genetic testing could help to unify the patient’s constellations of findings under a single diagnosis. Having the proper genetic diagnosis is important as the management strategies may differ when there are extracardiac issues to also consider. The growth, genitourinary, and cognitive issues associated with Noonan syndrome are all illustrated in this vignette. However, hematologic, oncologic, lymphatic, and other issues are also seen in patients with RASopathies and these could impact cardiac care.

A diagnosis of a genetic syndrome associated with HCM has significant implications for the patient. First, there are health supervision guidelines for a number of genetic syndromes associated with cardiac disease, including Noonan syndrome [32]. While some patients with Noonan syndrome have classic physical and facial features, it is not uncommon for Noonan

syndrome to be diagnosed in adolescents or young adults who were presumed to have isolated HCM.

Noonan syndrome and associated RASopathies are commonly associated with HCM. However, as opposed to cardiomyopathy caused by sarcomeric gene mutations, Noonan syndrome tends to also be associated with valvular issues which may require balloon valvuloplasty, surgery, or other intervention. Even individuals without any heart disease should continue to have periodic lifelong cardiac evaluation as cardiac findings can develop at any time. Intervals for cardiac evaluation need to take these factors into account.

Furthermore, as a large subset of Noonan syndrome is *de novo,* familial testing and screening strategies differ than in cases of familial isolated cardiomyopathy which are primarily due to autosomal dominantly inherited mutations in the sarcomeric genes. Evaluation of both parents is warranted with particular attention to the stereotypic features of Noonan syndrome. This may require referral to a clinical geneticist or other specialist. In cases that are due to a *de novo* mutation, testing or screening of siblings is not required.

Finally, the pathway dysregulated in Noonan syndrome, the RAS/MAPK signal transduction pathway, has effects that are distinct from those dysregulated by sarcomeric gene mutations. Some recent studies with Noonan mouse models have shown promising results in the reversal of HCM by pathway modulation, suggesting that therapeutic approaches more specific to this disease process may be on the horizon [33, 34].

Case 2

An 18-year-old male with HCM was seen in cardiology clinic. His family history was significant for a mother who was diagnosed with HCM at the age of 39. ECG showed sinus rhythm with evidence of preexcitation. There was T wave inversion in lateral and inferior leads and ST depression in lateral leads. Cardiac MRI showed severe hypertrophy with a maximal diastolic ventricular septal thickness of 34 mm. Delayed myocardial enhancement imaging demonstrated patchy areas of delayed enhancement. Genetic testing revealed a sarcomeric mutation.

The younger 17-year-old brother was subsequently also referred to cardiology. His ECG also showed preexcitation but was otherwise normal. Echocardiogram showed possible asymmetric hypertrophy, although quantitative measurements were very inconsistent and ranged from normal to abnormal. Based on clinical imaging it was unclear if this was the beginning of HCM or possibility normal hypertrophy in response to exercise as the younger brother was a soccer player. Mutation-specific genetic testing was sent in the brother.

This scenario illustrates the value of family-based genetic screening. In this particular case, it could help make the diagnosis HCM and inform recommendations regarding sports. In addition, it can also help identify other family member who may be at risk. Furthermore, for those that test negative it can remove the need for continued clinical screening.

Case 3

A six-year-old female was referred for heart transplant evaluation. She had initially presented at the age of four with congestive heart failure in the setting of presumed acute myocarditis. She also had marked liver and renal impairment initially which then gradually improved. On physical exam she had extreme failure to thrive with preserved height but weight dramatically below the fifth percentile. Her liver was enlarged 5 cm below the right costal margin. No other dysmorphic features were noted. ECG demonstrated normal sinus rhythm with first degree atrioventricular block, left axis deviation, left ventricular hypertrophy with strain pattern, T wave inversions with ST segment depression in the lateral leads, and possible biatiral enlargement. Transthoracic echocardiogram showed a severely dilated left ventricle with poor left ventricular function (ejection fraction 22–23%; normal 56–78%). Both atria were mildly dilated as was the right ventricle with borderline hypertrophy and mildly decreased function. She had mild-to-moderate tricuspid and mitral regurgitation. Right heart catheterization revealed elevated right heart pressures with high pulmonary vascular resistance at 7 Woods units x m^2. Cardiac biopsy pathology found storage material which was consistent with a polysaccharide. Based on suspicion for a glycogen storage disease specific genetic testing was sent.

This case demonstrates the etiological heterogeneity that exists especially within pediatric cardiomyopathy. In pediatrics, DCM is frequently thought to be due to myocarditis when in fact it could be due to an underlying genetic disease such as a neuromuscular disease, or, as in this case, a metabolic disorder. Moreover, at times it is difficult to distinguish if other organ system involvement is primary or secondary to the heart failure. In this particular scenario, a key component of the clinical management and an ongoing cardiac transplant evaluation was the molecular diagnosis. Knowledge of extracardiac disease could greatly alter medical decision making and the clinical treatment plan.

Summary

Pediatric cardiomyopathy poses unique challenges because it is rare and because its causes are more heterogeneous than adult cardiomyopathy. Genetic testing is an important component of the diagnostic evaluation of patients with cardiomyopathy and the risk stratification of the family members. Currently, cardiac management is directed toward the phenotype rather than being directed toward the underlying cause. For example, a patient with HCM would initially be treated similarly regardless of whether the underlying cause was Noonan syndrome, a mitochondrial disorder, or an *MYH7* mutation. Nevertheless, we know that a correct etiologic diagnosis is necessary to provide the optimal care for all the medical issues of the patient, to be proactive in healthcare supervision, and to apply appropriate family based cardiac and/or genetic screening to identify at risk family members. Therefore, genetic diagnosis plays an important role in overall patient management. Providing increasingly sophisticated, personalized approaches to cardiac management and therapy for disease is an active area of ongoing research and will require additional clinical longitudinal studies.

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Table 1

Summary of expert consensus recommendations from The Heart Rhythm Society and the European Heart Rhythm Association[18]

Classification is as follows: Class I “is recommended,” Class IIa “can be useful,” and Class IIb “may be considered.”

	Class I	Class IIa	Class IIb
Hypertrophic cardiomyopathy			
Patient with clinical diagnosis	X		
Cascade testing in family members	X		
Dilated cardiomyopathy			
Patient with familial disease		X	
Patient with clinical diagnosis and conduction disease and/or family history of premature sudden cardiac death	X		
Cascade testing in family members	X		
Left ventricular noncompaction cardiomyopathy			
Patient with clinical diagnosis		X	
Cascade testing in family members	X		
Restrictive cardiomyopathy			
Patient with clinical diagnosis			X
Cascade testing in family members	X		
Arrhythmogenic right ventricular cardiomyopathy			
Patient with clinical diagnosis		X	
Cascade testing in family members	X		